Original Article

Paravertebral block with morphine or dexmedetomidine as adjuvant to bupivacaine for post-operative analgesia in modified radical mastectomy: A prospective, randomised, double-blind study

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ABSTRACT

Background and Aims: General anaesthesia (GA) is the standard technique and paravertebral block (PVB) is suggested as an ideal analgesic in patients undergoing modified radical mastectomy (MRM). This study assessed post-operative analgesic efficacy of morphine or dexmedetomidine as adjuvant to bupivacaine in PVB. **Methods:** Forty-five women (18–60 years) undergoing MRM ± axillary clearance received PVB with 20 ml bupivacaine 0.25% with morphine 3 mg (Group BM) or dexmedetomidine 1 μg/kg (Group BD) in this prospective, randomised, double-blind study. After confirming the onset of PVB, standardised GA induction sequence was used. Intra-operative consumption of fentanyl and propofol along with postoperative morphine and diclofenac consumption, numerical rating scores (NRS) for pain at rest and on movement, nausea and vomiting scores, sedation scores and time to rescue analgesic were recorded. Chi-square or Fisher's exact test and Kruskal–Wallis followed by Mann–Whitney U-test were applied as applicable. **Results:** The number of patients requiring morphine during first 2-h post-operatively was significantly lower ($P = 0.006$) in Group BM. The mean dose of morphine in Group BM (0.84 [2.41] mg) and Group BD (1.70 [1.84] mg) was comparable ($P = 0.187$). NRS for pain at rest and on movement was significantly lower in Group BM at 2, 6, 12 and 18 h. The duration of analgesia was significantly prolonged in Group BM (1019.8 [422.9] min) than in Group BD (263.7 [194.9] min) ($P < 0.001$). **Conclusion:** Morphine is superior adjuvant to bupivacaine in PVB for modified radical mastectomy than dexmedetomidine.

Key words: Analgesia, bupivacaine, dexmedetomidine, mastectomy, modified radical, morphine, pain, post-operative

INTRODUCTION

Breast cancer is the most common cancer among women requiring surgical intervention.[1,2] Breast surgeries are usually performed under general anaesthesia (GA) and are frequently associated with severe post-operative pain, nausea and vomiting.[3] Pain if underestimated and untreated can be detrimental to the patients' homeostasis and recovery.[4] A variety of local and regional anaesthetic procedures which include local anaesthetic infiltration, field block, intercostal nerve blocks, brachial plexus blocks and thoracic epidural anaesthesia for breast surgery have been described[5] to avoid problems encountered with GA, reduce the post-operative hospital stay and for better outcome. Paravertebral block (PVB) can be

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considered as a well-established option to provide analgesia during breast surgery.[3]

Various adjuvants such as magnesium, clonidine, dexmedetomidine,[6] ketamine, dexamethasone[7] and opioids along with local anaesthetics have been used to enhance and prolong analgesia provided by PVB. Dexmedetomidine 1 μg/kg added to bupivacaine for PVB in patients undergoing breast cancer surgery under GA has been shown to prolong post-operative analgesia with decreased morphine[8] and tramadol[9] consumption. Morphine 2 mg with bupivacaine 0.25% in PVB has also been studied recently.[10]

We planned a prospective, randomised, double-blind study of PVB using morphine or dexmedetomidine as an adjuvant to bupivacaine in patients undergoing modified radical mastectomy (MRM) with or without axillary clearance. The aim of the study was to assess the analgesic efficacy of PVB during the first 24 h post-operatively.

METHODS

After obtaining approval from the Institutional Ethical Committee and written informed consent, women aged 18–60 years of the American Society of Anesthesiologists' Physical Status (ASA PS) I or II posted for elective MRM with or without axillary clearance for carcinoma breast in a tertiary care medical college hospital were included. Standard pre-anaesthetic evaluation was carried out a day before the surgery. Patients with bleeding disorders, allergy to local anaesthetics, infection at the injection site, psychiatric disorders, pregnant or breastfeeding women, body mass index ≥35 kg/m^2, Parkinson's disease, musculoskeletal disorders and those undergoing additional surgical procedure during the same surgical time were excluded from the study. The procedure was explained and the patients were educated about reporting on the 11-point numerical rating score (NRS) and post-operative nausea and vomiting (PONV) score. All the patients received oral diazepam 0.15 mg/kg and ranitidine 150 mg the night before surgery.

Computer-generated random numbers and sealed envelope method were used to randomise the patients into two groups in the pre-operative area: Group BM (20 ml of bupivacaine 0.25% with morphine 3 mg in PVB) and Group BD (20 ml of bupivacaine 0.25% with dexmedetomidine 1 μg/kg in PVB). An anaesthesiologist not involved in the study prepared the drug for PVB in a 20 ml syringe according to the randomisation. In the operating room, IV access was secured, IV fluid started at the rate of 20 ml/kg/h till the induction of anaesthesia and subsequently as per the fluid requirement calculated. Monitoring with electrocardiogram, non-invasive oscillometric blood pressure and pulse oximeter (SpO_2) were initiated.

Patients were placed in lateral position with the side to be blocked upward. The spinous process of T3 vertebra was identified and marked. Under aseptic precautions, at 2.5 cm lateral to the cephalad edge of the T3 spinous process, the skin, subcutaneous tissue and the periosteum of the transverse process of the T4 vertebra were infiltrated with 5 ml of lignocaine 1%. A 22G 10 cm insulated needle was introduced at 90° to the skin in all planes, at the site of local anaesthetic infiltration. The needle was advanced till it touched the transverse process of the vertebra, noting the depth. The needle was withdrawn and then advanced slightly caudad to walk off the transverse process for a distance of 1.0–1.5 cm. Initial setting of nerve stimulator was 1.5 mA current, 100 ms pulse width and 2 HZ frequency. Motor stimulation of intercostal muscles or paraesthesia in the respective area was elicited. The needle was repositioned till the best stimulation was achieved with a current strength 0.6 mA. The study drug (20 ml), as per the group allocation, was injected in small aliquots of 3–5 ml with repeated aspiration in between. Demonstration of analgesia to pinprick or inability to perceive cold sensation at the T1–T6 dermatome 15–20 min after the initiation of block was defined as successful PVB. Any complication or difficulty during the performance of PVB was noted.

Thereafter, GA was induced with IV fentanyl 2 μg/kg and propofol 2 mg/kg. Orotracheal intubation was facilitated by vecuronium 0.1 mg/kg and ventilation was controlled. Anaesthesia was maintained with propofol infusion 75–150 μg/kg/min and 50% nitrous oxide in oxygen. Mean arterial pressure (MAP) was maintained within 20% of the pre-operative baseline. Ramosetron 0.3 mg IV was administered after the induction of GA. Fentanyl 1 μg/kg/h was administered for procedures lasting more than 1 h. Any clinically perceived inadequate analgesia was treated with additional dose of fentanyl 1 μg/kg to keep the MAP within ± 20% of the baseline. No other analgesics were administered intra-operatively. IV ephedrine 6 mg was administered

as needed to keep MAP more than 60 mmHg. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine 50 + glycopyrrolate 10 μg/kg. Trachea was extubated on return of consciousness. Durations of anaesthesia and surgery, intra-operative consumptions of fentanyl and propofol were noted.

In the post-anaesthesia care unit (PACU), the patients were monitored for 2 h. Analgesia at rest and on movement was assessed at 30 min and at 1, 2, 6, 12, 18 and 24 h from the time of arrival to the PACU. Each patient was enquired about pain after surgery at rest as well as on moving the ipsilateral upper limb using an 11-point NRS where 0 = no pain and 10 = worst imaginable pain. If the patient complained of pain and NRS at rest was >3, IV morphine 0.05 mg/kg was administered every 15 min until NRS ≤3 during the PACU stay. The level of sedation and PONV were assessed on arrival to PACU, at 30 min, and at 1, 2, 6, 12, 18 and 24 h from the time of arrival to the PACU. The patients received IV diclofenac 75 mg as rescue analgesic when they complained of pain (NRS >3 at rest) in the ward and subsequently Q8 h. Morphine was not supplied in the ward as per our hospital policy. The duration of analgesia counted from the time of initiation of the PVB to the first analgesic request (NRS >3, either morphine in the PACU or diclofenac in the ward) was noted.

PONV was assessed on a 3-point scale where 0 = no nausea, no vomiting; 1 = nausea present, no vomiting; 2 = vomiting present with or without nausea. Ondansetron 4 mg IV was administered as rescue antiemetic if the PONV score is 1 or more and the time since the last dose of ondansetron is ≥8 h. Sedation was assessed using Ramsay Sedation Assessment Scale as follows – Awake Levels: patient anxious or agitated or both = 1; patient co-operative, oriented and tranquil = 2; patient responds to commands only = 3 and Asleep Levels: A brisk response to a light glabellar tap = 4, a sluggish response to a light glabellar tap = 5 and no response = 6.

The patients and the anaesthesiologists involved in the patient management intra-operatively and post-operative assessments were unaware of the group assignment.

The primary outcome assessed was requirement of IV morphine during the PACU stay. The secondary outcomes were analgesia assessed by NRS, the duration of analgesia, intra-operative fentanyl and propofol consumption, post-operative consumption of diclofenac, post-operative sedation scores, PONV, the incidence of PVB failure and the incidence of complications such as respiratory depression (respiratory rate <8/min), urinary retention, bradycardia (heart rate <50/min), vascular puncture, dural puncture and pneumothorax.

Patients who receive only GA are likely to require three times more supplemental narcotics in the post-operative period than those who receive PVB along with GA.[11] Estimating an average morphine requirement of 24 mg in the 24-h post-operatively and considering a 30% difference in morphine consumption between the groups to be clinically significant, a sample size of 17 patients in each group was estimated to achieve 80% power at 5% Type I error.

Continuous data are presented as mean (standard deviation [SD]) or median and interquartile range, as appropriate. For skewed data or ordinal data, Kruskal–Wallis test followed by Mann–Whitney U-test for two groups was applied. Qualitative or categorical variables are described as frequencies and proportions. Proportions were compared using Chi-square or Fisher's exact test whichever is applicable. $P < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS software version 20.0 (Statistical Packages for the Social Sciences, Chicago, IL).

RESULTS

Forty-seven patients were randomised into Group BM and Group BD. All the patients successfully received PVB as per the group allocation and underwent the procedure. One patient in Group BM was excluded because of protocol violation. One patient in Group BD was excluded as she underwent reexploration because of bleeding in the post-operative period [Figure 1].

The patient characteristics (age, body mass index, ASA and PS) and the side of surgery were comparable between the two groups [Table 1]. The durations of surgery and anaesthesia, intra-operative consumption of fentanyl and ephedrine were comparable between the two groups. However, the intra-operative consumption of propofol was significantly lower in Group BD (654.4 [217.1] mg, mean [SD]) than in Group BM (822.7 [305.4] mg), $P = 0.038$ [Table 2].

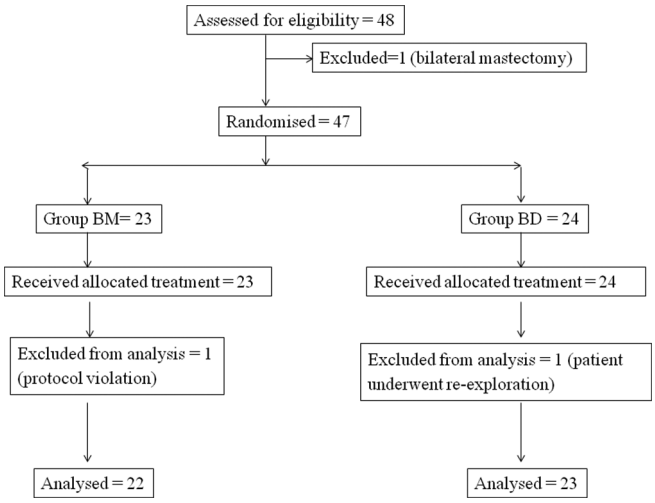

Figure 1: Group allocation and randomisation

In the PACU, the number of patients receiving IV morphine was significantly lower in Group BM (3 [13.6%]) than in Group BD (12 [52.2%]), $P = 0.006$. However, the total and the mean dose of IV morphine in Group BM (0.84 [2.41] mg) and Group BD (1.70 [1.84] mg) was comparable ($P = 0.187$). One of the patients in Group BM required 10 mg morphine in the PACU. The mean time for first rescue analgesic was significantly higher in Group BM (1019.8 [422.9] min) than Group BD (263.7 [194.9] min), $P < 0.001$. Diclofenac consumption in the ward in Group BM (85.2 [26.3] mg) was significantly lower than that in Group BD (192.4 [44.2] mg), $P < 0.001$.

There was no difference in pain scores between the two groups at rest and on movement at 30-min and 1-h post-operatively [Table 3]. However, patients in Group BM reported significantly lower pain scores at rest at 2 h ($P = 0.004$), 6 h ($P < 0.001$), 12 h ($P < 0.001$), 18 h ($P = 0.005$) and also on movement at 2 h ($P = 0.042$), 6 h ($P < 0.001$), 12 h ($P < 0.001$) and 18 h ($P = 0.001$) post-operatively as reflected in their NRS scores. Post-operative sedation and PONV scores [Table 4] were comparable between the two groups at all the time intervals. Rescue antiemetic was required for 6 patients in Group BM and 2 in Group BD (8 out of 45) in the first 24 h.

PVB failure, respiratory depression, urinary retention, bradycardia, vascular puncture, dural puncture and pneumothorax were not encountered.

DISCUSSION

In this study, we have demonstrated that the patients who received morphine as adjuvant in PVB experienced significantly better post-operative analgesia compared to dexmedetomidine at rest as well as on movement. The number of patients requiring IV morphine during their 2 h stay in PACU and post-operative consumption of diclofenac was significantly lower in Group BM. The duration of analgesia was also significantly prolonged in Group BM as assessed by the time of first rescue analgesic received by the patient. Even though the post-operative morphine consumption was lower in Group BM, it did not reach statistical significance.

A study[8] found that addition of dexmedetomidine 1 μg/kg to bupivacaine 0.5% for PVB in patients undergoing major breast cancer surgery under GA prolonged post-operative analgesia with decreased morphine consumption and lower incidence of nausea/vomiting compared to PVB with bupivacaine alone or no PVB. In a similar study,[9] dexmedetomidine 1 μg/kg added to 0.25% bupivacaine in PVB was shown to significantly prolong the mean time to first

Table 1: Patient characteristics

Parameters	Group BM (*n*=22)	Group BD (*n*=23)	*P*
Age (year)	48.4 (8.5)	49.5 (6.5)	0.767
ASA PS			
1/2*	16 (72.7)/6 (27.3)	17 (73.9)/6 (26.1)	0.928
BMI (kg/m^2)	24.31 (3.61)	22.69 (2.79)	0.100
Side of surgery (left/right)*	13 (59.1)/9 (40.9)	14 (60.9)/9 (39.1)	0.903

Values in mean (SD) and *n (%). ASA PS – American Society of Anesthesiologists Physical Status; BMI – Body mass index; SD – Standard deviation

Table 2: Intra-operative and post-operative data

Parameters	Group BM (*n*=22)	Group BD (*n*=23)	*P*
Duration of surgery (min)	146 (46)	131.3 (44.6)	0.284
Duration of anaesthesia (min)	188 (84)	160.7 (44.8)	0.177
Fentanyl consumption (μg)	224.6 (54.1)	207.6 (59.1)	0.322
Propofol consumption (mg)	822.7 (305.4)	654.4 (217.1)	0.038
Total ephedrine dose (mg)	3.8 (5.7)	4.7 (6.3)	0.626
Number of patients receiving morphine in PACU*	3 (13.6)	12 (52.2)	0.006
Morphine consumption in the PACU (mg)			
Total dose	18.5	39	0.187
Dose per patient	0.8 (2.4)	1.7 (1.8)	
Time for first analgesia (min)	1019.8 (422.9)	263.7 (194.9)	<0.001
Diclofenac consumption in the ward (mg)	85.2 (26.3)	192.4 (44.2)	<0.001
Post-operative ondansetron consumption (mg)	2.2 (4.4)	0.9 (2.9)	0.125

Values in mean (SD) and *n (%). PACU – Post-anaesthesia care unit; SD – Standard deviation

Table 3: Post-operative pain at rest and on movement assessed by numerical rating score at different intervals

Time	Group BM (*n*=22)		Group BD (*n*=23)		*P* (at rest)	*P* (on movement)
	At rest	On movement	At rest	On movement		
30 min	2 (0.5)	3 (0.5)	2 (1)	2.5 (0.63)	0.467	0.767
1 h	2 (0.25)	3 (0.5)	2 (0.5)	3 (0.5)	0.075	0.423
2 h	2 (0.63)	3 (0.75)	3 (1)	4 (1)	0.004	0.042
6 h	2 (0.13)	3 (0.13)	3 (0)	4 (0.5)	<0.001	<0.001
12 h	2.5 (0.5)	4 (0.5)	4 (0)	5 (0)	<0.001	<0.001
18 h	3 (0.63)	4.5 (0.5)	4 (0.5)	5 (0.5)	0.005	0.001
24 h	4 (0.5)	5 (0.5)	4 (0.5)	5 (0.5)	0.586	0.57

Values as median (IQR). IQR – Interquartile range

Table 4: Post-operative sedation and post-operative nausea and vomiting scores at different intervals

Time	Group BM (*n*=22)	Group BD (*n*=23)	*P*
Ramsay sedation score (1-6)*			
On arrival to PACU	3.0 (0)	3.0 (0)	0.419
30 min	2.5 (0.5)	2.0 (0.5)	0.307
1 h	2.0 (0)	2.0 (0)	0.975
2 h	2.0 (0)	2.0 (0)	1.000
6 h	2.0 (0)	2.0 (0)	1.000
12 h	2.0 (0)	2.0 (0)	1.000
18 h	2.0 (0)	2.0 (0)	1.000
24 h	2.0 (0)	2.0 (0)	1.000
PONV score (0/1/2)**			
On arrival to PACU	22 (100)/0/0	23 (100)/0/0	1.000
30 min	22 (100)/0/0	23 (100)/0/0	1.000
1 h	21 (95.5)/1 (4.5)/0	23 (100)/0/0	0.301
2 h	20 (90.9)/2 (9.1)/0	22 (95.6)/0/1 (4.4)	0.215
6 h	22 (100)/0/0	23 (100)/0/0	1.000
12 h	22 (100)/0/0	22 (95.6)/1 (4.4)/0	0.323
18 h	20 (90.9)/1 (4.5)/1 (4.5)	23 (100)/0/0	0.335
24 h	19 (86.3)/1 (4.5)/2 (9.1)	23 (100)/0/0	0.186

*Values as median (IQR) or **n (%). PONV – Post-operative nausea and vomiting; IQR – Interquartile range; PACU – Post-anaesthesia care unit

rescue analgesic (8.16 [6.42] h) as compared to 0.25% bupivacaine alone (6.48 [5.24] h), $P = 0.041$. The same was also longer than that found in the Group BD of our study (263.7 [194.9] min). The mean consumption of tramadol (194.44 [63.91] mg vs. 150.19 [76.98] mg, $P = 0.032$) for first 48 h was also significantly decreased. These differences could be because of the multiple injections method with 3–4 ml of the drug injected per level in their study. However, there was no significant difference in the pain scores at rest and on movement between the two groups.

In another study,[12] 48 patients were randomised into four groups of PVB: bupivacaine 0.5% with epinephrine, bupivacaine 0.25% with epinephrine, bupivacaine 0.25% with epinephrine with fentanyl 2 μg/ml and isotonic saline. The intra-operative fentanyl consumption, rescue analgesic consumption, as well as the cumulative pain scores at rest and on movement, was significantly less in the first 24 h in bupivacaine 0.25% with epinephrine with fentanyl and bupivacaine 0.5% with epinephrine and the average duration of analgesia was found to be 18 h in these two groups. However, bupivacaine 0.25% with epinephrine alone was associated with shorter duration of analgesia.

A recent study[10] compared bupivacaine 0.25%, bupivacaine 0.25% with dexmedetomidine 100 μg and bupivacaine 0.25% with morphine 2 mg in PVB performed using landmark-guided technique. The authors found that dexmedetomidine group had lower pain scores, prolonged analgesia, reduced post-operative pethidine consumption and more sedated patients compared to the other two groups. There are differences in the doses of dexmedetomidine (100 μg, fixed) and morphine (2 mg) used in the study compared to ours (1 μg/kg and 3 mg, respectively). Our results have shown that addition in PVB of morphine offers superior analgesic efficacy than dexmedetomidine. We performed PVB guided by nerve stimulation which is superior to the landmark-guided technique.

In our study, the overall incidence of PONV was low (18%) and comparable between the two groups at all times up to 24 h. The incidence of PONV in breast surgeries is said to range from 15% to 84% in the absence of prophylactic treatment. As per the study,[13] 20% of patients in the PVB group required medication for nausea and vomiting during their hospital stay compared with 39% in the GA group. Decreased incidence of PONV in our study may be attributed to PVB but the use of propofol, limiting the end-tidal nitrous oxide concentration to <50% and prophylaxis with a long-acting antiemetic like ramosetron could have added on to it.

In our study, we did not encounter respiratory depression, urinary retention, bradycardia and hypotension in any of the patients. Other techniques related rare complications associated with PVB such as pneumothorax, dural puncture and vascular puncture were also not encountered. PVB was successfully performed in all the 46 patients. A previous study concluded that success rates ranged from 75% to 90% regardless of the number of procedures performed previously[13] and PVB was easier to perform.[14] This could be attributed to the use of nerve stimulator-guided technique. Improved safety by the nerve stimulator-guided technique has been suggested in previous studies as well.[15]

We had confirmed the onset of the block by demonstrating the loss of cold sensation and pinprick in the corresponding dermatomes before induction of GA. In this study, intra-operative consumption of fentanyl and ephedrine was comparable between the two groups, but the dose of propofol was found to be significantly lower in Group BD in spite of the duration of surgery and anaesthesia being comparable. This could be because the PVB was performed by one of the two anaesthesiologists (blinded to group allocation) in all the cases, but the administration of GA was by different anaesthesiologists in few of the cases. Hence, it could have varied depending on the dosage of propofol infusion used by those anaesthesiologists even though the dose range was as per the protocol. Objective monitoring of the depth of anaesthesia with bispectral index or Entropy™ could have lead to a better titration of the dose of propofol and to more uniform administration of propofol in both the groups. Furthermore, paravertebral dexmedetomidine administration has been reported to reduce the intra-operative anaesthetic drug (including propofol) requirement.[16]

There are a few drawbacks of our study. There was a significant difference in the intra-operative propofol consumption between the two groups. This could have been avoided had the same anaesthesiologist conducted all the cases and depth of anaesthesia was monitored. Inclusion of a bupivacaine 0.25% alone group in the study could have given a better idea of the efficacy of bupivacaine in PVB and the adjuvants that were used. We could not use ultrasound for administration of PVB as the equipment was not available in our institute at the beginning of the study. Analgesia was assessed for 24 h duration in our study and whether the patients continued to have analgesia beyond that was not assessed. Klein *et al*.[10] suggested that PVB when compared to GA provides improved analgesia during the first 24 h after breast surgery and it may last as long as 72 h after the initial block.

As of now, there are no studies regarding the optimum dose of dexmedetomidine and morphine in PVB. A dose of dexmedetomidine more than 1 μg/kg in PVB may be associated with longer duration of analgesia and possibly, increased adverse events too.

CONCLUSION

Morphine is a better adjuvant to bupivacaine 0.25% during paravertebral block for postoperative analgesia in patients undergoing modified radical mastectomy with or without axillary clearance compared to dexmedetomidine.

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Conflicts of interest
There are no conflicts of interest.

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